DATA EVALUATION RECORD

INDAZIFLAM (BCS-AA10717)

Study Type: OPPTS 870.3100 [§82-1a]; Subchronic Oral Toxicity Study in Mice

Work Assignment No: 5-1-203 B (MRID 47443288)

Prepared for
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DATA EVALUATION RECORD

STUDY TYPE: 90-Day Oral Toxicity [feeding]-mice; OPPTS 870.3100 [§82-1a] (rodent); OECD 408.

PC CODE: 080818 **DP BARCODE:** D356856
TXR #: 0054980

TEST MATERIAL (PURITY): Indaziflam (96.5% a.i.)

SYNONYMS: AE 1170437; BCS-AA10717; N-[(1R,2S)-2,6-dimenthyl-2,3-dihydro-1H-inden-1-yl]-6-[(1R)-1-fluoroethyl]-1,3,5-triazine-2,4-diamine

CITATION: McElligott, A. (2005) AE 1170437: 90-day toxicity study in the mouse by dietary administration. Bayer CropScience, Sophia Antipolis Cedex, France. Laboratory Study No.: SA 04094, February 28, 2005. MRID 47443288. Unpublished.

SPONSOR: Bayer AG, Bayer CropScience, Alfred Nobel Str. 50, Monheim, Germany

EXECUTIVE SUMMARY: In a subchronic oral toxicity study (MRID 47443288), indaziflam (AE 1170437; 96.5% a.i.; Lot/Batch No. BCTM1130-2) was administered in the diet to 10 C57BL/6J mice/sex/dose at dose levels of 0, 100, 500, or 1200 ppm (equivalent to 0/0, 19/23, 91/118, and 218/256 mg/kg/day in males/females) for 13 weeks.

No adverse, treatment-related effects were observed on clinical chemistry, organ weights, or gross or microscopic pathology.

At 1200 ppm, one female was moribund sacrificed on Day 10. No clear cause of death could be determined, but this death was presumed to be due to treatment. This female exhibited hunched posture and wasted appearance, and one male also exhibited hunched posture. These findings were not observed in any other animal on the study. Body weights were decreased ($p<=0.01$) by 9-19% in both sexes throughout treatment. Weekly cumulative body weight gains were also decreased ($p<=0.05$) throughout treatment in both sexes. Overall body weight gain was decreased ($p<=0.01$) by 45-59% in both sexes. Decreased food consumption was observed throughout treatment in males (decr 3-17%) and females (decr 14-29%). Decreases in food consumption were significant ($p<=0.05$) at all time points in females, but only on Days 57, 85, and 90 in males.

The LOAEL was 1200 ppm (equivalent to 218/256 mg/kg/day in males/females), based on increased mortality and wasted appearance in females, increased hunched posture in both sexes, and decreased body weights, body weight gains, and food consumption in both sexes. The NOAEL was 500 ppm (equivalent to 91/118 mg/kg/day in males/females).

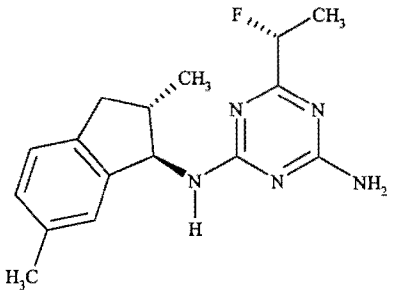
This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3100; OECD 408) for a subchronic oral toxicity study in the mouse.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, Flagging, and Quality Assurance statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: AE 1170437

Description:	White solid
Lot/Batch No.:	BCTM1130-2
Purity (w/w):	96.5% a.i. (99.6% total isomer)
Stability of compound:	The Sponsor stated that the test compound was stable in the diet for at least 92 days at room temperature.
CAS #:	730979-19-8 (AE 1170437 isomer); 950782-86-2 (BCS-AA 10717 – total isomers)
Structure:	

2. Vehicle: Diet

3. Test animals

Species:	Mouse
Strain:	C57BL/6J
Age and weight at study initiation:	Approximately 6 weeks of age; 16.1-20.5 g males and 14.3-17.1 g females
Source:	Charles Rivers Laboratories, ST. Germain-sur-L'Arbesle Cedex, France
Housing:	Individually in suspended stainless steel wire mesh cages
Diet:	Certified rodent chow A04C-10 PI, powdered and irradiated (Scientific Animal Food and Engineering, Augy, France), *ad libitum*, except before blood collection when animals were fasted overnight
Water:	Filtered and softened municipal supplied tap water, *ad libitum*
Environmental conditions	
Temperature:	20 - 24°C
Humidity:	40 -70 %
Air changes:	10-15/hr
Photoperiod:	12 hours light/12 hours dark
Acclimation period:	13 days

B. STUDY DESIGN

1. In life dates: Start: May 25, 2004; End: August 25, 2004

2. Animal assignment: The animals were randomly assigned, while ensuring that individual body weights were within 20% of the mean body weight for each sex, to the test groups shown in Table 1.

TABLE 1: Study design[a]			
Test group	Dose to animal (ppm)	Compound intake (mg/kg/day in M/F)	No. rats/sex killed at Week 13
Control	0	0/0	10
Low	100	19/23	10
Mid	500	91/118	10
High	1200	218/256	10

a Data were obtained from pages 3 and 9 of the study profile.

3. **Dose-selection rationale:** The dose levels were selected based on the results from a previous 14-day dietary study in the mouse (SA03279), where dietary administration of up to 2000 ppm in males and females resulted in reduced mean body weight in both sexes, reduced food consumption in females, and reduced alkaline phosphatase activity in females at the end of treatment. A dose level of 700 ppm represented the No Observed Effect Level in males and females.

4. **Treatment preparation, administration, and analysis:** Appropriate amounts of the test substance were ground to a fine powder and incorporated into the diet by dry mixing to achieve the desired concentrations. Diet preparations were made approximately every 7 weeks and were stored at room temperature. Homogeneity (bottom, middle, and upper strata) of AE 1170437 in the diet at 100 and 1200 ppm of the first diet preparations was evaluated. In a previous study[1], the stability of the test substance at 20 and 10,000 ppm in the diet was confirmed for up to 92 days at room temperature (data not presented). Concentration checks at the three doses of the diet preparations were also measured in the first batch (as the mean of the homogeneity measurements), and in each preparation from the second batch.

Results

Homogeneity (range as % nominal): 93-108%

Concentration (range as % nominal): 93-99%

The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the animals was acceptable, provided that the cited stability study did indicate that the test compound was stable under conditions of the study.

5. **Statistics:** Group means were compared at the 5% and 1% levels of significance. Statistical analyses were performed using the Path/Tox system V4.2.2 (Module Enhanced Statistics).

PARAMETER	STATISTICAL ANALYSES
Body weights Body weight gain Terminal body weight Food consumption Organ weights Clinical chemistry	Bartlett's test was performed on the data, followed by ANOVA (parametric) or Kruskal-Wallis (nonparametric), as appropriate. When a significant difference occurred, Dunnett's test (parametric) or the Dunn test (nonparametric) was performed (2-sided). A log transformation was used on body weight and food consumption data if a significant difference ($p \leq 0.05$) was detected using Bartlett's test on non-transformed data.

[1] L. GUTIERREZ (SA 04029) (2004): AE 1170437, Stability in rodent diet. Analytical pre-study, Bayer CropScience, Sophia-Antipolis, France.

These statistical analyses were considered appropriate if the normality of data distribution was confirmed prior to parametric testing.

C. METHODS

1. Observations

1a. Cageside observations: All animals were checked for moribundity and mortality twice daily (once daily on weekends or public holidays). Observed clinical signs were recorded at least once daily for all animals during the study.

1b. Clinical examinations: Detailed physical examinations were performed at least weekly during the treatment period.

1c. Neurological evaluations: Neurotoxicity was not evaluated in this study. Neurotoxicity and motor activity were tested in the rats in the concurrently submitted subchronic toxicity study (MRID 47443287), as well as concurrently submitted subchronic and acute neurotoxicity studies (MRIDs 47443309 and 47443310, respectively).

2. **Body weight:** Each animal was weighed prior to treatment, on the first day of test substance administration, at least weekly throughout the treatment, and before necropsy (at which time the animals were diet fasted overnight). Cumulative mean body weight gains were reported weekly; mean body weight gain/day was also reported weekly.

3. **Food consumption and compound intake:** The daily average food consumption was calculated per animal (g/animal/day) and was reported weekly. Compound intake (mg/kg bw/day) values were calculated from the nominal dietary test material concentration, food consumption, and body weight data.

4. **Ophthalmoscopic examination:** Ophthalmoscopic examinations were not performed.

5. **Hematology and clinical chemistry:** Hematology was not performed. Blood was collected from all animals on Days 91, 92, or 93, prior to necropsy, by puncture of the orbital sinus. The mice were diet fasted overnight and anesthetized by inhalation of isoflurane. The CHECKED (X) parameters were examined.

a. Hematology

	Hematocrit (HCT)*		Leukocyte differential count*
	Hemoglobin (HGB)*		Mean corpuscular HGB (MCH)*
	Leukocyte count (WBC)*		Mean corpuscular HGB concentration (MCHC)*
	Erythrocyte count (RBC)*		Mean corpuscular volume (MCV)*
	Platelet count*		Reticulocyte count
	Blood clotting measurements*		Cell morphology
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Recommended for 90-day oral rodent studies based on Guideline 870.3100

b. Clinical chemistry

	ELECTROLYTES		OTHER
	Calcium	X	Albumin*
	Chloride		Creatinine*
	Magnesium	X	Urea nitrogen*
	Phosphorus	X	Total cholesterol*
	Potassium*		Globulins
	Sodium*		Glucose*
	ENZYMES (more than 2 hepatic enzymes eg., *)	X	Total bilirubin
X	Alkaline phosphatase (ALP)*, n=2-5	X	Total protein (TP)*
	Cholinesterase (ChE)		Triglycerides
	Creatine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)		Albumin/globulin ratio
X	Alanine aminotransferase (ALT/also SGPT)*, n=4-10		
X	Aspartate aminotransferase (AST/also SGOT)*, n=8-10		
	Sorbitol dehydrogenase*		
	Gamma glutamyl transferase (GGT)*, n=0-1		
	Glutamate dehydrogenase		

* Recommended for 90-day oral rodent studies based on Guideline 870.3100

6. **Urinalysis**: Urinalysis was not performed, but is optional under Guideline 870.3100.

7. **Sacrifice and pathology**: On Days 91-93, all surviving animals were sacrificed by exsanguination under deep anesthesia (inhalation of Isoflurane). An approximately equal number of animals randomly distributed amongst all groups were sampled on each day at the dosing phase and recovery sacrifice. Animals were diet fasted overnight prior to sacrifice. All animals, including decedents, were necropsied. The CHECKED (X) tissues were collected for histological examination, and the (XX) organs were also weighed (paired organs weighed together).

	DIGESTIVE SYSTEM
X	Tongue
X	Salivary glands*
X	Esophagus*
X	Stomach*
X	Duodenum*
X	Jejunum*
X	Ileum*
X	Cecum*
X	Colon*
X	Rectum*
XX	Liver*+
X	Gall bladder (not rat)*
	Bile duct (rat)
X	Pancreas*
	RESPIRATORY
X	Trachea*
X	Lung*
X	Nose*
X	Pharynx*
X	Larynx*

	CARDIOVASC./HEMAT.
X	Aorta*
XX	Heart*+
X	Bone marrow*
X	Lymph nodes*
XX	Spleen*+
XX	Thymus*+
	UROGENITAL
XX	Kidneys*+
X	Urinary bladder*
XX	Testes*+
X	Epididymides*+
X	Prostate*
X	Seminal vesicles*
XX	Ovaries*+
XX	Uterus*+
X	Mammary gland*
X	Vagina

	NEUROLOGIC
XX	Brain*+ (with brain stem)
X	Peripheral nerve*
X	Spinal cord (3 levels)*
X	Pituitary*
X	Eyes (optic nerve)*
	GLANDULAR
XX	Adrenal gland*+
X	Lacrimal gland
X	Parathyroid*
X	Thyroid*
	OTHER
X	Bone (femur and sternum)
X	Skeletal muscle
X	Skin*
X	All gross lesions and masses*

* Recommended for 90-day oral rodent studies based on Guideline 870.3100
\+ Organ weights required for rodent studies.

Samples were fixed by immersion in neutral buffered 10% formalin with the exception of the eye, optic nerve, Harderian gland, epididymis, and testis which were fixed in Davidson's fixative.

All of the above mentioned samples (except exorbital lachrymal gland, larynx/pharynx, and nasal cavities) were embedded in paraffin wax, sectioned, and stained with hematoxylin and eosin. Histological sections were prepared routinely and examined from the following samples: all samples from the control and 1200 ppm groups; and liver, kidney, lung, thyroid gland samples, and macroscopic findings from the 100 and 500 ppm groups. Following the initial histopathological examination, a peer review of representative slides was performed by a second pathologist, and reported results represent the consensus opinion of the two pathologists.

II RESULTS

A. OBSERVATIONS

1. **Mortality:** One 1200 ppm female was moribund sacrificed on Day 10. A body weight loss of 4 g was noted in this animal between Days 1-8 and corresponded to a reduced food consumption of 1.9 g/day compared to a mean of 3.3 g/day for the 1200 ppm group during the same period. This animal had a hunched posture and wasted appearance from Day 8 until sacrifice. No clear cause of death could be determined. One control male was found dead on Day 85, and an ileum torsion was considered to be the cause of death. All other animals survived until sacrificed.

2. **Observations:** Hunched posture was noted in one mouse/sex at 1200 ppm (vs 0 in the other groups). The same female that had hunched posture was also wasted in appearance (vs 0 in the other groups) and was moribund sacrificed. No other clinical signs were reported that were related to treatment.

B. BODY WEIGHT AND BODY WEIGHT GAIN: At 1200 ppm, decreased ($p \leq 0.01$) body weights were observed throughout treatment in males (↓9-16%) and females (↓11-19%; Table 2). Body weights were similar to controls in the other treated groups. Weekly cumulative body weight gains were also decreased ($p \leq 0.05$) throughout treatment in both sexes at 1200 ppm and transiently at 500 ppm. Overall body weight gain was decreased at 1200 ppm (↓45-59%; $p \leq 0.01$), but only slightly decreased at 500 ppm (↓8-11%; not statistically significant [NS]).

TABLE 2. Mean (±SD) body weights and body weight gains (g) in mice orally treated with AE 1170437 for 90 days [a]

Day (s)	Dose (ppm)			
	0	100	500	1200
Males				
1	18.2±1.4	18.3±1.1	18.2±1.2	18.2±1.2
8	19.7±1.1	19.6±1.0	19.3±1.0	17.9±1.4** (↓9)
43	23.3±1.0	23.1±0.6	22.9±0.7	20.4±1.6** (↓12)
85	26.2±0.9	25.6±1.3	25.0±1.1	22.1±2.1** (↓16)
90	26.3±0.9	26.0±1.1	25.5±1.0	22.8±2.2** (↓13)
BWG (1 to 90)	8.2±0.8	7.6±1.0	7.3±1.0 (↓10)	4.5±1.7** (↓45)
Females				
1	16.0±0.9	16.1±0.6	16.0±0.8	16.1±0.7
8	16.9±1.1	16.9±1.0	16.2±0.7	15.0±1.3** (↓11)
43	20.5±1.0	20.5±0.9	20.0±0.8	16.6±1.2** (↓19)
90	22.1±0.9	22.3±0.8	21.6±0.6	18.6±1.4** (↓16)
BWG (1 to 90)	6.1±0.6	6.3±0.7	5.6±0.9 (↓8)	2.5±1.0** (↓59)

a Data (n=9-10) were obtained from Tables 2-3 on pages 36-45 of the study report. Percent difference from controls is included in parentheses and was calculated by the reviewers.

** Significantly different ($p \leq 0.01$) from the control groups

C. FOOD CONSUMPTION AND COMPOUND INTAKE

1. **Food consumption:** At 1200 ppm, decreased food consumption was observed throughout treatment in males (↓3-17%) and females (↓14-29%; Table 3). Decreases were significant ($p \leq 0.05$) at all time points in females, but only on Days 57, 85, and 90 in males. The only other difference ($p \leq 0.05$) between treated groups and controls was an increase in food consumption in the 100 ppm males on Day 50 (unrelated to dose).

TABLE 3. Mean (±SD) food consumption (g) in mice orally treated with AE 1170437 for 90 days [a]

Day (s)	Dose (ppm)			
	0	100	500	1200
Males				
8	3.4±0.3	3.6±0.3	3.5±0.4	3.3±0.3 (↓3)
57	4.6±0.7	4.5±0.3	4.4±0.5	3.8±0.5** (↓17)
85	4.5±0.4	4.6±0.2	4.3±0.6	3.8±0.6* (↓16)
90	4.6±0.5	4.8±0.4	4.4±0.6	3.9±0.7* (↓15)
Females				
8	3.5±0.5	3.6±0.3	3.9±0.3	3.0±0.6* (↓14)
85	5.1±0.6	5.2±0.8	4.8±0.5	3.6±0.6** (↓29)
90	4.9±0.6	5.0±0.6	5.2±0.6	3.9±0.6** (↓20)

a Data (n=9-10) were obtained from Table 5 on pages 51-55 of the study report. Percent difference from controls is included in parentheses and was calculated by the reviewers.
* Significantly different ($p \leq 0.05$) from the control groups
** Significantly different ($p \leq 0.01$) from the control groups

2. **Compound consumption:** Compound intake values (mg/kg/day) are presented in Table 1 of this DER.

D. **CLINICAL CHEMISTRY:** No adverse, treatment-related effect was observed in the clinical chemistry parameters. At 1200 ppm compared to controls, decreased ($p \leq 0.01$) albumin was observed in the males (↓14%), and decreased ($p \leq 0.01$) total protein concentration was noted in the females (↓13%). Increased ($p \leq 0.05$) aspartate aminotransferase was observed in the 1200 ppm females (↑38%). These differences were not considered adverse due to the slight magnitude of change and lack of corroborating pathological evidence of a treatment-related effect.

E. SACRIFICE AND PATHOLOGY

1. **Organ weight:** No adverse, treatment-related effect was observed on organ weights. At 1200 ppm, mean terminal body weights were decreased ($p \leq 0.01$) by 13-14% in both sexes when compared to controls. Absolute, relative to body, and relative to brain spleen weight was decreased in females (↓19-29%); however, there was no other pathological finding that suggested an adverse effect. Therefore, this finding was considered incidental. Other slight differences (≤25%) in organ weights were noted in the brain, heart, liver, and kidneys of both sexes; however, as there were no histopathologic correlates noted in any of these organs, these differences were most likely attributable to the decreased terminal body weights of the animals, rather than the result of test article toxicity on the organs themselves. The weights of other organs in the treated groups were similar to controls.

2. **Gross pathology:** No adverse, treatment-related effect was observed on the incidence of gross lesions. In the spleen, an increased incidence of black focus(i) was noted in the 1200 ppm males (5/10 treated vs 2/10 controls), which may have corresponded to the microscopic observation of an increased incidence of focal/multifocal increased melanin pigment (4/10 treated vs 2/10 controls). However, there was no other pathological evidence of abnormalities in the spleen. Consequently, this effect was not considered adverse.

3. **Microscopic pathology:** No adverse, treatment-related effect was observed on the incidence of microscopic lesions (Table 4). A decreased incidence of minimal to slight corticoepithelial vacuolation (focal/multifocal) was noted in the kidneys in the 500 (5/10 treated vs 8/10 controls) and 1200 (0/10 treated) ppm males. There was no further pathological evidence to suggest an adverse effect, and this finding was of only minimal severity in 7 of the controls; therefore, this condition was not considered adverse. An increased incidence of minimal to slight hepatocellular vacuolation (mainly centrilobular, diffuse) was observed in the 500 (6/10 treated vs 4/10 controls) and 1200 (9/10 treated) ppm females. Only a minor increase ($p \leq 0.01$) in relative to body liver weight (↑11%) was noted in these animals. Without further evidence indicative of hepatotoxicity, the increased incidence of hepatocellular vacuolation was not considered adverse. In light of the lack of major liver effects in the rat studies, it is likely that the vacuolization is more related to liver activity in response to the presence of the chemical rather than frank toxicity.

   Diffuse lymphoid hyperplasia (3/10) and plasmacytosis (2/10) were noted in the submaxillary lymph node in the 1200 ppm males compared to 0/10 controls, but these observations were considered incidental. The incidence of unilateral focal tubular degeneration in the testes was increased at 1200 ppm (5/10 treated vs 2/10 controls), but this finding was considered incidental because it was unilateral and without corroborating pathological evidence of toxicity. The incidences of all other findings in the treated groups were similar to controls.

TABLE 4. Selected microscopic findings (# affected/10) in mice treated with AE 1170437 for 90 days [a]

Observation		Dose (ppm) 0	100	500	1200
Males					
Kidney					
Corticoepithelial vacuolation: focal/multifocal	Total	8	6	5	0
	Minimal	7	6	5	0
	Slight	1	0	0	0
Females					
Liver					
Hepatocellular vacuolation: mainly centrilobular, diffuse	Total	4	3	6	9
	Minimal	4	3	5	3
	Slight	0	0	1	6

a Data were extracted from pages 10-11 of the study profile.

III. DISCUSSION AND CONCLUSIONS

A. **INVESTIGATOR'S CONCLUSIONS:** The Sponsor stated that the LOAEL was 1200 ppm. At this dose, one animal was considered to have died due to treatment and had a wasted appearance and hunched posture. Decreased body weight, body weight gain, and food consumption were noted. Decreased serum albumin concentration was noted in males, and a tendency towards lower total serum protein was observed in the females.

B. **REVIEWER'S COMMENTS:** No adverse, treatment-related effects were observed on clinical chemistry, organ weights, or gross or microscopic pathology.

One 1200 ppm female was moribund sacrificed on Day 10. No clear cause of death could be determined, but this death was presumed to be due to treatment. This female exhibited hunched posture and wasted appearance, and one 1200 ppm male also exhibited hunched posture. These findings were not observed in any other animal on the study. Additionally at 1200 ppm, decreased ($p \leq 0.01$) body weights were observed throughout treatment in males (↓9-16%) and females (↓11-19%). Weekly cumulative body weight gains were also decreased ($p \leq 0.05$) throughout treatment in both sexes at 1200 ppm and transiently at 500 ppm. Overall body weight gain was decreased at 1200 ppm (↓45-59%; $p \leq 0.01$), but only slightly decreased at 500 ppm (↓8-11%; NS). In the absence of corroborating evidence of toxicity at 500 ppm, the minor effects on body weight gain were not considered adverse. At 1200 ppm, decreased food consumption was observed throughout treatment in males (↓3-17%) and females (↓14-29%). Decreases in food consumption were significant ($p \leq 0.05$) at all time points in females, but only on Days 57, 85, and 90 in males.

No adverse, treatment-related effect was observed in the clinical chemistry parameters. At 1200 ppm compared to controls, decreased ($p \leq 0.01$) albumin was observed in the males (↓14%), and decreased ($p \leq 0.01$) total protein concentration was noted in the females (↓13%). These differences were not considered adverse due to the slight magnitude of change and lack of corroborating pathological evidence of a treatment-related effect.

The LOAEL was 1200 ppm (equivalent to 218/256 mg/kg/day in males/females), based on increased mortality and wasted appearance in females, increased hunched posture in both sexes, and decreased body weights, body weight gains, and food consumption in both sexes. The NOAEL was 500 ppm (equivalent to 91/118 mg/kg/day in males/females).

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3100; OECD 408) for a subchronic oral toxicity study in the mouse.

C. **STUDY DEFICIENCIES:** The following deficiencies were noted but do not change the conclusions of this DER:

- Test compound stability data in the diet were not provided.
- Hematology parameters were not evaluated, nor were the following clinical chemistry parameters: potassium, sodium, creatinine, and glucose levels. However, no treatment-related findings were noted on hematology and clinical chemistry parameters in the rat up to

doses of 10,000 ppm in a concurrently submitted subchronic toxicity study (MRID 47443287).